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Juvenile Rheumatoid Arthritis in Velo-Cardio-Facial Syndrome: Coincidence or Unusual Complication?

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We report on two patients with velo-cardio-facial syndrome (VCFS) and juvenile rheumatoid arthritis (JRA). The first, a 9-year-old girl, presented with microcephaly, characteristic face, congenital heart disease, and velopharyngeal insufficiency. Fluorescence in situ hybridization (FISH) study showed deletion of D22S75 (N25), confirming the diagnosis of VCFS. At age 7, she developed joint pain, and polyarticular JRA was diagnosed. Awareness of this case led to the subsequent diagnosis of VCFS (also confirmed by FISH) in another, unrelated 12-year-old girl with characteristic face, hypernasal speech, and obesity. JRA was first diagnosed in this case at age 5 years, and she subsequently developed severe polyarticular disease. Neither patient had clinical or laboratory evidence of immunodeficiency. This observation represents the first report of the association of JRA with VCFS and raises the question of whether this is a coincidental association or a rare complication of this condition.

KEY WORDS: velo-cardio-facial syndrome, DiGeorge anomaly, juvenile rheumatoid arthritis, chromosome 22q11.2 deletion, autoimmune disease

INTRODUCTION

The past several years have focused on defining the clinical phenotype attributable to 22q11.2 deletions [Scambler et al., 1991, 1992; Driscoll et al., 1992, 1993; Goldberg et al., 1993; Goldmuntz et al., 1993; Lindsay et al., 1995; Morrow et al., 1995]. To this end, we describe two unrelated patients, each having juvenile rheumatoid arthritis (JRA) and velo-cardio-facial (Shprintzen) syndrome (VCFS) [Shprintzen et al., 1978]. These observations suggest that JRA may be associated with VCFS.

MATERIALS AND METHODS

Clinical Reports

Case 1 (Fig. 1). CF was born via emergency Cesarean section for breech presentation and fetal distress at 36 weeks gestation after an uncomplicated pregnancy. Congenital heart disease was noted shortly after birth, and at age 4 years she underwent repair of a membranous ventricular septal defect (VSD), resection of infundibular pulmonary stenosis, and ligation of a patent ductus arteriosus. She underwent palatal pushback at age 4 years for velopharyngeal insufficiency, and because of continued problems, she underwent sphincter pharyngoplasty and tonsillectomy at age 6 years with some improvement in her symptoms.

Her past medical history was significant for scoliosis and a leg length discrepancy. Neurological evaluation confirmed a learning disability, and an MRI showed slightly diminutive basifrontal and anterior temporal lobes and a type-II Arnold-Chiari malformation. Psychomotor development was delayed; at age 8 11/12 years, she was estimated to be ~1½ years behind her classmates.

No other relatives are affected with VCFS (Fig. 2). CF's mother (II-2) had scoliosis with low back pain in her teenage years and had onset of arthralgias in her feet and wrists in her fourth decade. She has been evaluated by a rheumatologist, and her antinuclear antibody (ANA) titer initially was negative, but recently has become positive (titer 1:80, speckled pattern). Rheumatoid factor is negative, and no specific diagnosis has been made. CF's maternal cousin (III-6) had a VSD, but no other signs of VCFS. There are no other individuals in the family with rheumatologic disease.

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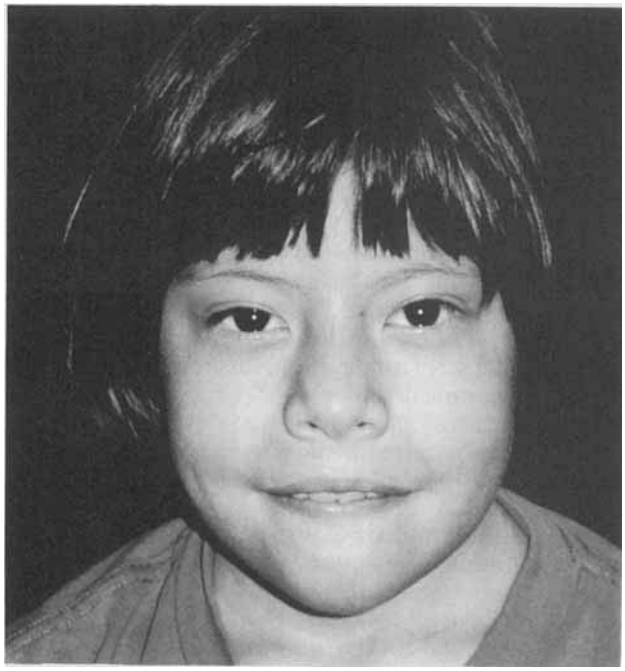

Fig. 1. Case 1 at age 9 5/12 years.

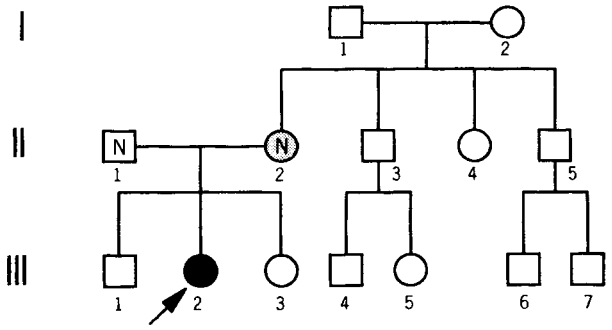

Fig. 2. Pedigree (case 1). Completely filled symbol depicts individual with deletion of 22q11.2 by FISH analysis, symbols with "N" depict individuals with no deletion of 22q11.2 by FISH analysis. Gray-colored symbol indicates individual with onset of arthralgias in the fourth decade, but no specific rheumatologic diagnosis has been made (see text).

The patient was first evaluated at age 6 5/12. At that time her height was 110.6 cm (10th centile), weight was 18.2 kg (10th centile), and head circumference was 47 cm (<2nd centile). She was an alert, cooperative child with hypernasal speech. She had epicanthal folds, small ears with thick, firm superior helices, and a prominent nose with a bulbous tip and hypoplastic nasal alae. Palate was high-arched with scarring from her previous palatal surgery. She had a grade II/VI holosystolic murmur, a small umbilical hernia, and long, slender fingers. The diagnosis of VCFS was made at this time.

Joint pain developed at age 7 years, involving her knees, ankles, hips, and wrists. Results of rheumatologic studies are summarized in Table I. In addition, antibodies to *Crithidia,* RNP, SM, and dsDNA were negative, and streptococcal antibody titers (ASO, anti-DNAse B, anti-A carbohydrate) were also negative. Immunologic studies including serum IgG, IgM and IgA, and T-cell subset studies were normal. A diagnosis of polyarticular JRA was made. Serial eye examinations have shown no evidence of uveitis.

When seen again in Genetics clinic at age 8 10/12 years, her physical examination was basically unchanged except for her limbs. Range of motion at her wrists was very limited, but no swelling or warmth was noted. She had mild to moderate swelling and warmth to the touch at her ankles bilaterally, with mild limitation in range of motion.

Case 2 (Fig. 3). This 11-year-old caucasian girl (SC) was born by uneventful spontaneous vaginal delivery after an uncomplicated pregnancy. The baby developed a raspy, crouplike cry on the fourth day of life. At age 14 months, she was evaluated because of a weak, hoarse voice, and obesity. Direct laryngoscopy and broncho-

TABLE I. Rheumatologic Studies on Cases 1 and 2

Study	Case 1	Age when study done	Case 2	Age when study done
Antinuclear antibody (ANA)	Positive (1:160 homogenous)	7 yr	Positive (1:10,240 homogenous)	6 yr
	Positive (1:80 speckled)	9 3/12 yr	Positive (1:320 homogenous)	8 yr
	Positive (1:80 speckled)	9 1/2 yr	—	
Rheumatoid factor	Negative	7 yr	Negative	6 yr
	Positive (1:80)	9 yr	Negative	8 yr
	Positive (1:160)	9 1/2 yr	—	
Erythrocyte sedimentation rate (ESR) (normal 0–20 mm/hr)				
Mean	40 mm/hr (n = 18)	—	67 mm/hr (n = 7)	—
Range	6–172 mm/hr	—	45–103 mm/hr	—

Fig. 3. Case 2 at age 4 9/12 years.

scopy documented normal vocal cords but presence of a 20% subglottic stenosis. At age 3 years, she underwent tonsillectomy and adenoidectomy for mild obstructive sleep apnea. At age 5, she developed painful, red, swollen knees and ankles and morning stiffness, and evaluation suggested pauciarticular JRA as the probable diagnosis. Results of ANA, rheumatoid factor, and ESR are summarized in Table I. C3 was 199 and 167 (normal: 88–155 mg/dL) and C4 was 29.5 and 22 (normal: 12–32 mg/dL). C-reactive protein, HLA-B27 Ag, antibodies to dsDNA, *Crithidia,* Sm, RNP, Scl-1, SSA/la, SSB/ro, ANA centromere, and Lyme disease were all negative. Streptococcal antibody titers (ASO, anti-DNAse, anti-A carbohydrate) were also negative. Immunologic studies including serum IgM and IgA, and T-cell subset studies were normal, except for an elevated IgG of 2382 mg/dl (normal 736–1,900). Initially she had normal range of motion of all her large joints but had crepitus in her elbows. Thereafter she developed persistent joint involvement, with progression to severe elbow contractures with ankylosis and decreased range of motion of all large joints. She was treated with nonsteroidal anti-inflammatory agents, physical therapy, and occupational therapy. An ophthalmology exam showed no uveitis. An echocardiogram was normal. Developmental testing revealed mild mental delay.

The proposita is one of three affected sibs (Fig. 4). Her parents were nonconsanguineous. At the time of birth, her mother was 21 and father 33 years old. The mother (II-6) was developmentally normal, but the father (II-5) reportedly did not speak until about 4 years old and had a speech impediment in later childhood. He now has normal speech and is physically healthy without abnormal facial appearance. The father has two sons by a previous union; both are said to have normal speech and one has pectus excavatum (III-1). A paternal aunt (II-1) has mental retardation, reportedly attributed to congenital toxoplasmosis. The paternal grandmother (I-2), now 60 years old, developed severe rheumatoid arthritis at about age 40 years. Both paternal grandparents have normal speech and have no known heart defects or learning problems, but have thus far been unavailable for 22q deletion testing. The proposita's two full sibs (III-4 and III-5) are also affected with VCFS, but neither has developed any joint problems or illnesses suggestive of an autoimmune disorder.

When examined at age 10 8/12 years SC was a quiet girl with an open-mouthed facial appearance, poor articulation, and apparent hypernasality of speech. Her height was 155.5 cm (>95th centile), weight was 88 kg (>95th centile), and OFC was 59 cm (>98th centile). Pertinent findings included protruding, simply developed ears, strabismus of the right eye, mild epicanthal folds, hypoplastic nasal alae, prominent upper central incisors, micrognathia with overbite, severe obesity, and tapered fingers. She had limited range of motion at both elbows and had moderate finger contractures, as well as a waddling gait with pronated feet. Her joints were not swollen, erythematous or tender to palpation, but she had decreased range of motion in almost all large and small joints.

Cytogenetic/FISH Studies

High-resolution (extended) chromosomes were prepared from peripheral blood lymphocyte cultures by ethidium bromide treatment following modifications of the procedure described by Ikeuchi [1984]. Chromosomes were G-banded (GTG) following modifications of the procedure described by Seabright [1971]. Chromosome spreads were hybridized with digoxigenin-labeled DNA probes D22S75 and D22S39 (control probe) following the procedure outlined by the probe manufacturer (ONCOR). Signal detection was achieved with Rhod-

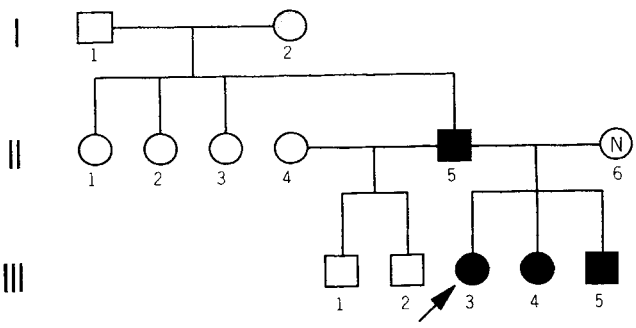

Fig. 4. Pedigree (case 2). Completely filled symbols depict individuals with deletion of 22q11.2 by FISH analysis, symbol with "N" depicts individual with no deletion of 22q11.2 by FISH analysis. Gray-colored symbol indicates individual with severe rheumatoid arthritis with onset at about age 40 years (not yet tested for 22q deletion).

amine and FITC conjugated antidigoxigenin. Chromosomes were either propidium iodide or DAPI counterstained. FISH images were digitally captured utilizing CytoProbe Imaging Software (Applied Imaging).

RESULTS

Cytogenetic/FISH Studies

Karyotypes prepared and examined for both patients and parents, as well as sibs of Case 2, demonstrated apparently normal karyotypes. Specific high resolution analysis of the chromosome 22 critical region of 22q11.2 at resolution levels of 550 or greater bands per haploid set of chromosomes did not definitively demonstrate a cytogenetic deletion or rearrangement. FISH study with the D22S75 (N25) DNA probe indicated that this specific DNA segment was deleted from one chromosome 22 homologue in both cases presented, as well as in the father (II-5) and 2 sibs (III-4 and III-5) of Case 2. Normal hybridization of the D22S75 probe was seen in both parents of Case 1 (II-1 and II-2) and the mother of Case 2 (II-6). All cells scored for the FISH analysis demonstrated successful hybridization of the control probe (D22S39).

DISCUSSION

We report on two patients with VCFS, confirmed by FISH analysis to have deletions of chromosome 22q11.2, with JRA. Both patients meet currently accepted diagnostic criteria for JRA [Brewer et al., 1977; Cassidy et al., 1986]. This is the first report of a rheumatologic disease in a patient with VCFS, DiGeorge anomaly (DGA), or other conditions associated with deletions of 22q. Other studies of large numbers of VCFS patients have not noted rheumatologic disease as a complication [Goldberg et al., 1993], so the possibility that this is a coincidental finding must be considered. Of note, both our cases have family members with joint problems, so perhaps our cases were at an increased risk of JRA for genetic reasons not related to VCFS. The frequency of VCFS has not been well documented; one estimate has placed this at 1 in 10,000 [Kelly et al., 1993], but this may be an underestimate. Population studies have established the prevalence of JRA at ~1 in 1,000 children [Gäre and Fasth, 1992; Towner et al., 1993]. Even if one considers the frequency of VCFS to be twice that estimated by Kelly et al. [1993], the frequency of observing a single case with both JRA and VCFS, assuming they are independent events, would be 1 in 5 million. The observation of two such cases in our center would be unlikely, since the population we serve includes <1 million children.

Chromosome abnormalities associated with inflammatory arthropathies have recently been reviewed [Ihnat et al., 1993], and the only case involving chromosome 22 was a patient in the fourth decade with onset of ankylosing spondylitis and rheumatoid arthritis found to have the Philadelphia chromosome on cytogenetic studies of bone marrow [Heath and Moloney, 1965]. We were unable to find any purported chromosome locus associated with JRA, other than its association with certain HLA antigens [Hoffman et al., 1986; Odum et al., 1986, Lipnick and Tsokos, 1990].

Other autoimmune conditions have been observed in patients with DGA or VCFS. These include a patient with DGA and mosaicism for a chromosome 22q deletion with autoimmune thyroid disease (Graves disease) [Ham Pong et al., 1985], two patients with DGA and autoimmune hemolytic anemia and thrombocytopenia [Pinchas-Hamiel et al., 1994; Sherry et al., 1990], and one patient with VCFS and hypothyroidism [Goldberg et al., 1993], although information regarding autoantibodies on this latter patient was not noted.

Thymus-dependent immunity has been shown to be abnormal in DGA, and based on the degree of T-cell deficiency, patients have been divided into partial and complete forms of DGA. Whereas immunodeficiency is seen in the complete form, dysfunctional T-cell regulation is seen in milder forms of DGA [Müller et al., 1989], possibly related to abnormal T-suppressor cell function [Durandy et al., 1986]. Selective antibody deficiency has been noted in "familial" DiGeorge cases having low CD4 counts, again implicating a T-cell regulatory problem [Schubert and Moss, 1992].

T-cell regulation also may play an important role in the development of JRA. Abnormal T-suppressor cell function has been found in children with JRA, but this abnormality is reversible, with improvement during periods of clinical remission [Silverman et al., 1990]. Hypergammaglobinemia and autoantibody production seen in JRA, suggestive of abnormal B-cell regulation, may also implicate T-cell dysfunction in the pathogenesis of JRA [see Lipnick and Tsokos, 1990 for review]. The term "autogene" has been coined to refer to immunoregulatory genes that, when altered, may predispose an individual to development of autoimmune disease [Mountz and Talal, 1993]. If autoimmune disorders are proven to be associated with microdeletions in the 22q11 region, one could postulate that this region contains an "autogene," which could contribute to the causation of autoimmune disease, comparable to the role of oncogenes in cancer [Miller et al., 1990]. Neither of our patients had clinical evidence of immunodeficiency, and their immunologic studies, including serum immunoglobulins and T-cell subset studies were normal, with the exception of an elevation in IgG in Case 2, most likely an indication of her ongoing inflammatory process [Bluestone et al., 1970]. However, our patients may still have subtle abnormalities in their T-cell populations that contributed to development of JRA.

In conclusion, the finding of JRA in two patients with VCFS suggests that the clinical spectrum of this condition may include inflammatory arthropathies. Further reports of cases of rheumatologic disease and VCFS will be necessary to confirm this association.

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